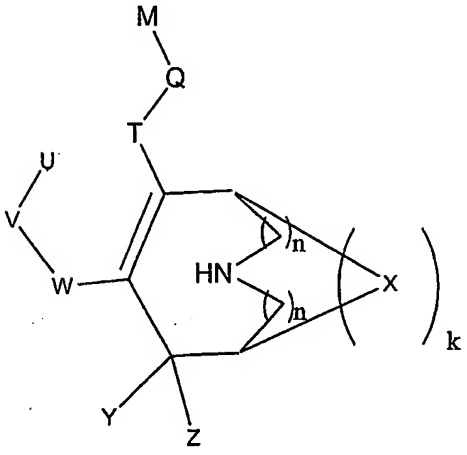
Claims

1. Compounds of the general formula I



Formula I

wherein

Y and Z represent independently from each other hydrogen, fluorine or a methyl group, or Y and Z may together form a cyclopropyl ring; in case k represents the integer 1, Y and Z both represent hydrogen;

X represents $-(CH_2)_m$-N(L)-$(CH_2)_m$-; $-CH_2$-CH(K)-CH_2-; $-CH_2CH_2$-; $-CH_2OCH_2$-; $-CH_2SCH_2$-; $-CH_2SOCH_2$-; $-CH_2SO_2CH_2$-; -CO-NL-CO-; -CO-NL-CHR^6-; $-CHR^6$-NL-CO-;

W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

V represents a bond; $-(CH_2)_r$-; -A-$(CH_2)_s$-; $-CH_2$-A-$(CH_2)_t$-; $-(CH_2)_s$-A-; $-(CH_2)_2$-A-$(CH_2)_u$-; -A-$(CH_2)_v$-B-; $-CH_2-CH_2-CH_2$-A-CH_2-; -A-CH_2-CH_2-B-CH_2-; $-CH_2$-A-CH_2-CH_2-B-; $-CH_2-CH_2-CH_2$-A-CH_2-CH_2-; $-CH_2-CH_2-CH_2-CH_2$-A-CH_2-; -A-CH_2-CH_2-B-CH_2-CH_2-; $-CH_2$-A-CH_2-CH_2-B-CH_2-; $-CH_2$-A-$CH_2-CH_2-CH_2$-B-; or $-CH_2-CH_2$-A-CH_2-CH_2-B-; –O-CH_2-$CH(OCH_3)$-CH_2-O; -O-CH_2-$CH(CH_3)$-CH_2-O-; -O-CH_2-$CH(CF_3)$-CH_2-O-; -O-CH_2-$C(CH_3)_2$-CH_2-O-; -O-CH_2-$C(CH_3)_2$-O-; -O-$C(CH_3)_2$-CH_2-O-; -O-CH_2-$CH(CH_3)$-O-; -O-$CH(CH_3)$-CH_2-O-; -O-CH_2-$C(CH_2CH_2)$-O-; -O-$C(CH_2CH_2)$-CH_2-O-;

A and B independently represent -O-; -S-; -SO-; $-SO_2$-;

U represents aryl; heteroaryl;

T represents -CONR^1-; $-(CH_2)_p$OCO-; $-(CH_2)_p$N(R^1)CO-; $-(CH_2)_p$N(R^1)SO_2-; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^5$; heteroaryl-$O(CH_2)_vR^5$; aryl-$O(CH_2)_vO(CH_2)_wR^5$; heteroaryl-$(CH_2)_vO(CH_2)_wR^5$; aryl-$OCH_2CH(R^7)CH_2R^5$; heteroaryl-$OCH_2CH(R^7)CH_2R^5$;

L represents -R^3; -COR^3; -$COOR^3$; -$CONR^2R^3$; -SO_2R^3; -$SO_2NR^2R^3$;

-$COCH(Aryl)_2$;

K represents –H; -CH_2OR^3; -$CH_2NR^2R^3$; -$CH_2NR^2COR^3$; -$CH_2NR^2SO_2R^3$; -CO_2R^3; -$CH_2OCONR^2R^3$; -$CONR^2R^3$; -$CH_2NR^2CONR^2R^3$; -$CH_2SO_2NR^2R^3$; -CH_2SR^3; -CH_2SOR^3; -$CH_2SO_2R^3$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

R^5 represents –OH, lower alkoxy, -$OCOR^2$, -$COOR^2$, -$NR^2R^{2'}$, -$OCONR^2R^{2'}$, -$NCONR^2R^{2'}$, cyano, -$CONR^2R^{2'}$, SO_3H, -$SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH^2$, -$NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^6 represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be unsubstituted or monosubstituted with hydroxy, -$CONH_2$, -COOH, imidazoyl, -NH_2, -CN, -$NH(NH)NH_2$;

R^7 represents -OH, OR^2; $OCOR^2$; $OCOOR^2$; or R^6 and R^5 form together with the carbon atoms to which they are attached a 1,3-dioxolane ring which is substituted in position 2 with R^2 and $R^{2'}$; or R^6 and R^5 form together with the carbon atoms to which they are attached a 1,3-dioxolan-2-one ring;

k is the integer 0 or 1;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0; in case n represents the integer 1, m is the integer 0; in case k represents the integer 0, n represents the integer 0; in case X does not represent $-(CH_2)_m$-N(L)-$(CH_2)_m$-, n represents the integer 0;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 1, 2, 3, or 4;

w is the integer 1 or 2;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

2. Compounds according to claim 1, wherein

Y and Z represent independently from each other hydrogen, fluorine or a methyl group, or Y and Z may together form a cyclopropyl ring;

X represents $-CH_2-CH(K)-CH_2-$; $-CH_2CH_2-$; $-CH_2OCH_2-$; $-CH_2SCH_2-$; $-CH_2SOCH_2-$; $-CH_2SO_2CH_2-$; $-CO-NL-CHR^6-$; $-CHR^6-NL-CO-$;

W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

V represents a bond; $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$; $-O-CH_2-CH(OCH_3)-CH_2-O$; $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-CH(CF_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$; $-O-CH_2-C(CH_3)_2-O-$; $-O-C(CH_3)_2-CH_2-O-$; $-O-CH_2-CH(CH_3)-O-$; $-O-CH(CH_3)-CH_2-O-$; $-O-CH_2-C(CH_2CH_2)-O-$; $-O-C(CH_2CH_2)-CH_2-O-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^8$; heteroaryl-$O(CH_2)_vR^8$; aryl-$O(CH_2)_vO(CH_2)_wR^8$; heteroaryl-$(CH_2)_vO(CH_2)_wR^8$; aryl-$OCH_2CH(R^7)CH_2R^5$; heteroaryl-$OCH_2CH(R^7)CH_2R^5$;

L represents -R^3; -COR^3; -$COOR^3$; -$CONR^2R^3$; -SO_2R^3; -$SO_2NR^2R^3$;

-$COCH(Aryl)_2$;

K represents –H; -CH_2OR^3; -$CH_2NR^2R^3$; -$CH_2NR^2COR^3$; -$CH_2NR^2SO_2R^3$; -CO_2R^3; -$CH_2OCONR^2R^3$; -$CONR^2R^3$; -$CH_2NR^2CONR^2R^3$; -$CH_2SO_2NR^2R^3$; -CH_2SR^3; -CH_2SOR^3; -$CH_2SO_2R^3$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

R^5 represents –OH, lower alkoxy, -$OCOR^2$, -$COOR^2$, -$NR^2R^{2'}$, -$OCONR^2R^{2'}$, -$NCONR^2R^{2'}$, cyano, -$CONR^2R^{2'}$, SO_3H, -$SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^6 represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be unsubstituted or monosubstituted with hydroxy, -$CONH_2$, -COOH, imidazoyl, -NH_2, -CN, -$NH(NH)NH_2$;

R^7 represents -OH, OR^2; $OCOR^2$; $OCOOR^2$; or R^6 and R^5 form together with the carbon atoms to which they are attached a 1,3-dioxolane ring which is substituted in position 2 with R^2 and $R^{2'}$; or R^6 and R^5 form together with the carbon atoms to which they are attached a 1,3-dioxolan-2-one ring;

R^8 represents lower alkoxy;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 1, 2, 3, or 4;

w is the integer 1 or 2;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

3. Compounds according to anyone of claims 1 to 2 wherein

X represents $-CH_2CH_2-$.

4. Compounds according to anyone of claims 1 to 3 wherein

T represents $-CONR^1-$;

Q represents methylene;

M represents aryl-$O(CH_2)_vR^8$; heteroaryl-$O(CH_2)_vR^8$; aryl-$OCH_2CH(R^7)CH_2R^5$; heteroaryl-$OCH_2CH(R^7)CH_2R^5$.

5. Compounds according to anyone of claims 1 to 4 wherein

R^1 represents cycloalkyl;

R^8 represents lower alkoxy

v represents 3.

6. Compounds according to anyone of claims 1 to 5 wherein

W represents a 1,4-disubstitueted phenyl.

7. Compounds according to anyone of claims 1 to 6 wherein

U is a mono-, di-, or trisubstituted phenyl whereby the substituents are halogen; lower alkyl or lower alkoxy.

8. Compounds according to anyone of claims 1 to 7 wherein

U is a mono-, di-, or trisubstituted phenyl whereby the substituents are selected from fluorine and chlorine.

9. Compounds according to anyone of claims 1 to 8 wherein
V represents -A-$(CH_2)_s$-.

10. Compounds according to anyone of claims 1 to 9 wherein
A represents –O-, and
s represents 3.

11. The compounds according to any one of claims 1 - 9 selected from the group consisting of
(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-methoxypropoxy)-3-methylpyridin-4-ylmethyl]amide.

12. A pharmaceutical composition containing at least one five-membered heteroaryl derivative according to any of claims 1 to 11 and pharmaceutically acceptable carrier materials or adjuvants.

13. A compound according to any of claims 1 to 11, or composition according to claim 12, for use as medicament.

14. Use of a compound according to any of claims 1 to 11, or a composition according to claim 12, for the manufacture of a medicament for the treatment or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.

15. A method for the treatment or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system, comprising the administration to a patient of a pharmaceutically active amount of a five-membered heteroaryl derivative according to any of claims 1 to 11, or composition according to claim 12.